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09/779,560	02/09/2001	Marianne Harboe	58982.000002	6162

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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 03/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/779,560	HARBOE, MARIANNE	
	Examiner	Art Unit	
	David J Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,6,9-14,16-18,29-31,35,36,39,42 and 43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,6,9-14,16-18,29-31,35,36,39,42 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 February 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/3/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 1, 5-6, 9-14, 16-18, 29-31, 35-36, 39, and 42-43 are pending in the application.

[2] Applicants' amendment to the claims, filed January 03, 2005, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[3] Applicants' arguments filed January 03, 2005 have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[4] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Specification/Informalities

[5] The objection to the specification in the use of the trademarks "Hannilase™, "Thermolase™," and "Modilase™" is maintained for the reasons of record as set forth at item [5] of the Office action mailed 10/01/2004.

RESPONSE TO ARGUMENT: Applicants argue "the specification properly sets forth the terms noted in the Office Action." However, as applicants have failed to amend the specification to capitalize the disclosed trademarks, the objection is maintained.

Claim Rejections - 35 USC § 112, Second Paragraph

[6] The rejection of claim(s) 1, 5-6, 9-14, 16-18, 29-31, 35-36, 39, and 42 under 35 U.S.C. 112, second paragraph, as set forth at items [7]-[8] of the Office action mailed 10/01/2004 is withdrawn in view of the amendment to the claims.

In order to clarify the record, it is noted that claim 16 has been amended to recite a pH value of "approximately 1.8." In this case, the term "approximately" has been interpreted as being fully synonymous with the term "about." However, as claim 16 depends from and includes all limitations of claim 1, the medium of the method of claim 16 cannot be subjected to a pH greater than 1.99 or less than 1.0, *i.e.,* the pH of the medium of claim 16 has an upper limit of 1.99 and a lower limit of 1.0. As such, it is the examiner's position that claim 16 is clear in the meaning of "approximately 1.8."

[7] Claims 6, 9-12, and 35-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] In a previous Office action, the examiner raised a rejection under 35 U.S.C. 102(b), citing the reference of Uren et al. (see pp. 5-6 of the Office action mailed 10/1/04). In setting forth reasoning for the rejection, the examiner asserted that *E. coli* inherently expressed a glucoamylase polypeptide (see, *e.g.,* p. 5 of the Office action mailed 10/1/04). In the instant response, applicants more than once stress the point that Uren et al. does not teach a medium comprising glucoamylase activity. This prompted the examiner to search the prior art for a reference providing evidence that *E. coli* endogenously expresses a glucoamylase polypeptide. However, the examiner was not readily able to locate such prior art teachings. The specification and the prior art provide

evidence for glucoamylase expression in *Aspergillus niger* var. *awamori*. However, the evidence of record fails to provide an indication that other organisms as recited in the claims endogenously express a glucoamylase polypeptide, such that the cultivation of the organism generates a medium comprising glucoamylase activities. Similar reasoning applies to chymosin and those organisms that do not endogenously express chymosin. As such, claims 6, 9-12, and 35-36 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the alteration of an organism that does not endogenously express chymosin and/or glucoamylase, the alteration of an animal species, a mammalian species including a ruminant species including a bovine species, an ovine species, a caprine species, a deer species, a buffalo species, an antelope species, a giraffe species, and a *Camelidae* species including *Camelus dromedarius*, a porcine species, an *Equidae* species, a primate species, a plant species, a bacterial species including gram negative and gram positive bacterial species, a yeast species, a *Saccharomyces cerevisiae,* a methylotrophic yeast species, a *Klyuveromyces* species including *Klyuveromyces lactis*, a *Cryphonectria* species, a *Fusarium* species, a *Rhizomucor* species, an *E. coli,* a *Bacillus*, or a *Pichia pastoris* cell such that a "medium...is derived from the cultivation" of the cell or organism that comprises chymosin and glucoamylase activities. In the absence of endogenous expression of a polypeptide having chymosin and/or glucoamylase activities in these organisms, it is unclear as to how such activities are present in the

medium derived from their cultivation. Without such an active method step, the claimed method is incomplete.

It is noted that if applicants provide evidence for the presence or expression of glucoamylase in bovine stomach, claims 1, 5-6, 9, 13-14, 16-18, and 29-31 will likely be rejected under 35 U.S.C. 102(b) as being anticipated by Larsen et al. (WO 95/29999; cited in the Office action mailed 4/9/2002).

[b] Claim 31 is indefinite in the recitation of "chymosin activity is naturally produced in a mammalian species" as it is unclear as to the characteristics that distinguish a chymosin activity that is naturally produced in a mammalian species from a chymosin activity that is naturally produced in a non-mammalian species or a chymosin activity that is not "naturally" produced at all. It is suggested that applicants clarify the meaning of the term.

Claim Rejections - 35 USC § 112, First Paragraph

[8] The new matter rejection of claims 1, 5-6, 9-14, 16-18, 29-31, 35-36, 39, and 42 under 35 U.S.C. 112, first paragraph, as set forth at item [9] of the Office action mailed 10/01/2004 is withdrawn in view of the amendment to the claims.

[9] It is noted that claims 1, 5-6, 9-14, 16-18, 29-31, 35-36, 39, and 42-43 in their currently amended form have not yet been rejected under 35 U.S.C. 112, first paragraph, for lack of adequate written description. However, upon further consideration of the requirements of 35 U.S.C. 112, first paragraph, claims 1, 5-6, 9-14, 16-18, 29-31, 35-36, 39, and 42-43 are rejected under 35 U.S.C. 112, first paragraph, as containing

subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 (claims 5, 13-14, 16-18, and 43 dependent therefrom) is drawn to a method of providing a milk clotting composition using a genus of media that comprises chymosin activity and glucoamylase activity. Claims 6, 9-12, 35-36, and 42 limit the source of the genus of media of claim 1. Claims 29-31 and 39 limit the chymosin activity of claim 1 to being derived from a particular species of mammal.

In order to clarify the record, it is noted that the term "chymosin activity" or "glucoamylase activity" has been interpreted by the examiner as meaning chymosin enzymatic activity exhibited by a chymosin polypeptide or glucoamylase enzymatic activity exhibited by a glucoamylase polypeptide, respectively. Also, the term "subjecting said medium to a pH" in claim 1 has been interpreted as meaning adjusting or changing the pH of the entire medium "having a pH of 2.0 or higher" to a pH "in the range of 1.0 to 1.99." Further, it is noted that the term "derived" as used in claims 6, 9, 29, and 31 has been clarified by applicant (see pp. 6-7 of the response filed 10/9/02) as meaning "to...obtain from a source of origin." See also items 6-7 at p. 2 of the Declaration of Peter Budtz, filed 10/9/02.

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical

and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In this case, the specification discloses only a single representative species of the genus of recited media, *i.e.,* a medium produced by culture of *Aspergillus niger* var. *awamori* expressing a recombinant bovine pro-chymosin-glucoamylase fusion protein. While the specification fails to disclose the method of obtaining or making the pro-chymosin-glucoamylase fusion protein, the examiner assumes that this fusion protein is constructed according to the method of Ward et al. (*Biotechnol* 8:435-440, particularly pp. 439-440; cited in the IDS filed 4/16/2001). If this is incorrect, applicants are requested to clarify the record. Other than this single working example of the genus of recited media, the specification fails to disclose any other species of a medium that comprises chymosin activity and glucoamylase activity. While it is noted the specification discloses sources of media comprising chymosin, *e.g.,* the media of cultured microorganisms recombinantly expressing chymosin and the extract of bovine stomach (see particularly pp. 7-8 of the specification), there is no evidence of record that these media further comprise glucoamylase activity as required in the claims.

While MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus", it also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus". In the instant case, the claimed genus of media encompasses species that are widely

variant, including the "media" from the cultivation of any animal or plant species. The genus is also widely variant with respect to the structures of the polypeptides that exhibit chymosin activity, particularly in view of the specification's disclosure that the method is applicable to "preparations of aspartic proteases derived from a naturally produced aspartic protease by the addition or deletion of one or more amino acids or substituting one or more amino acids herein" (p. 8, lines 33-35 of the specification). The specification fails to disclose the structure of even a single representative species of the structure of a mutant or variant chymosin that can be used to practice the claimed invention. Given the lack of description of a representative number of species, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[10] It is noted that claims 1, 5-6, 9-14, 16-18, 29-31, 35-36, 39, and 42-43 in their currently amended form have not yet been rejected under 35 U.S.C. 112, first paragraph, for lack of an enabling disclosure. However, upon further consideration of the requirements of 35 U.S.C. 112, first paragraph, claims 1, 5-6, 9-14, 16-18, 29-31, 35-36, 39, and 42-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of providing a milk clotting composition comprising the steps of: (i) culturing *Aspergillus niger* var. *awamori* expressing a recombinant pro-chymosin-glucoamylase fusion protein as disclosed by Ward et al. (cited in the IDS filed 4/16/2001) and collecting the medium obtained therefrom and (ii) subjecting said medium to a pH in the range of 1.0 to 1.99 for a time sufficient to

inactivate at least 50% of the glucoamylase activity while maintaining at least 75% of said chymosin activity, does not reasonably provide enablement for the broad scope of claimed methods, particularly with respect to the scope of media that is provided comprising chymosin and glucoamylase activities. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

It is the examiner's position that undue experimentation would be required for a skilled artisan to make and/or use the entire scope of the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

(A) The breadth of the claims: Claim 1 (claims 5, 13-14, 16-18, and 43 dependent therefrom) broadly encompasses a method of providing a milk clotting composition using any media from any source that comprises chymosin activity and glucoamylase activity. Claim 6 broadly encompasses the method of claim 1, wherein the media is derived from the cultivation of any organism that during its cultivation produces

chymosin and glucoamylase activities. Claims 9-12, 35-36, and 42 broadly encompass the method of claim 1, wherein the media is derived from the cultivation of species of organisms, including specifically recited species. Claims 29-31 and 39 broadly encompass the method of claim 1, wherein the chymosin activity is derived from a particular species of mammal. It should be noted that the chymosin activity is not limited to those chymosin polypeptides that are known in the art, but further encompasses "preparations of aspartic proteases derived from a naturally produced aspartic protease by the addition or deletion of one or more amino acids or substituting one or more amino acids herein" (p. 8, lines 33-35 of the specification). The scope of the claims is not commensurate in scope with the enablement provided by the specification. In this case, the specification is enabling only for a method of providing a milk clotting composition comprising the steps of: (i) culturing *Aspergillus niger* var. *awamori* expressing a recombinant pro-chymosin-glucoamylase fusion protein as disclosed by Ward et al. (cited in the IDS filed 4/16/2001) and collecting the medium obtained therefrom and (ii) subjecting said medium to a pH in the range of 1.0 to 1.99 for a time sufficient to inactivate at least 50% of the glucoamylase activity while maintaining at least 75% of said chymosin activity.

(B) The nature of the invention: The nature of the invention involves exploiting the differential pH stabilities of chymosin and glucoamylase such that treatment of a medium comprising chymosin and glucoamylase at pH of 1.0 to 1.99 reduces glucoamylase activity, while maintaining chymosin activity. The invention is dependent

upon the structures of the chymosin and glucoamylase polypeptides present in the medium.

(C) The state of the prior art; (D) The level of one of ordinary skill; and (E) The level of predictability in the art: Regarding the source of medium comprising chymosin and glucoamylase, as noted above, while the specification and the prior art provide evidence for endogenous glucoamylase expression in *Aspergillus niger* var. *awamori,* there is no evidence of record that other organisms as recited in the claims endogenously express a glucoamylase polypeptide, such that the cultivation of the organism generates a "medium" comprising chymosin and glucoamylase activities, particularly those mammalian and plant species. Also, it is noted that there is no evidence of record in the specification or prior art for the use of a glucoamylase fusion protein in species of bacteria or yeast. While one of skill in the art would have the ability to express a pro-chymosin-glucoamylase fusion protein using bacteria or yeast as an expression host, introducing a heterologous glucoamylase activity into the medium of these microorganisms would not appear to be the "best mode" for carrying out the invention, particularly as the specification describes glucoamylase activity as an "undesired enzymatic side activity" (p. 5, bottom of the specification).

Regarding the chymosin and glucoamylase activities, as noted above, the invention is dependent upon the structures of the chymosin and glucoamylase polypeptides as the structure of the polypeptides determines their ability to maintain activity or lose activity at a certain level of pH. The use of a medium comprising a mutant chymosin, *e.g.,* mutants or variants of bovine chymosin or chymosin from

sources other than cow, will not necessarily be useful in practicing the invention. For example, Li et al. (*Biochem Biophys Acta* 1384:121-129; cited in the Office action mailed 10/1/2004) teach pH-sensitive mutants of bovine chymosin. As evidenced by the specification (p. 8, lines 33-35 of the specification), the claims encompass the use of any mutant or variant chymosin. The encoded amino sequence of a polypeptide determines the protein's structural and functional properties. Predictability of which changes can be tolerated in an encoded protein's amino acid sequence and obtain the desired activity/utility requires a knowledge of and guidance with regard to which nucleotides in the encoding nucleic acid or amino acids in the encoded protein's sequence, if any, are tolerant of modification and which are conserved (*i.e.*, expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. The positions within a protein's sequence where modifications can be made with a reasonable expectation of success in obtaining a polypeptide having the desired activity/utility are limited in any protein and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, *e.g.,* multiple substitutions. At the time of the invention, methods for isolating or generating variants and mutants of a given nucleic acid were known in the art. However, the specification provides no guidance for altering any chymosin polypeptide with an expectation of obtaining a polypeptide that has the desired alleged activity/utility. The state of the art at the time of the invention provides evidence for the high level of unpredictability in altering a polypeptide sequence with an expectation that

the polypeptide will maintain the desired activity/utility. For example, Branden et al. ("Introduction to Protein Structure", Garland Publishing Inc., New York) teach "[p]rotein engineers frequently have been surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes" and "[t]he often surprising results of such experiments reveal how little we know about the rules of protein stability... ...they also serve to emphasize how difficult it is to design *de novo* stable proteins with specific functions" (page 247). The teachings of Branden et al. are evidenced by the reference of Witkowski et al. (*Biochemistry* 38:11643-11650), which teaches that only a single amino acid substitution results in conversion of the parent polypeptide's activity from a beta-ketoacyl synthase to a malonyl decarboxylase (see *e.g.*, Table 1, page 11647).

(F) The amount of direction provided by the inventor and (G) The existence of working examples: The specification provides only a single working example of the claimed method, *i.e.,* a method of providing a milk clotting composition comprising the steps of: (i) culturing *Aspergillus niger* var. *awamori* expressing a recombinant bovine pro-chymosin-glucoamylase fusion protein and collecting the medium obtained therefrom and (ii) subjecting said medium to a pH in the range of 1.0 to 1.99 for 20 minutes or 21 hours. While the specification fails to disclose the method of obtaining or making the pro-chymosin-glucoamylase fusion protein, the examiner assumes that this fusion protein is constructed according to the method of Ward et al. (*Biotechnol* 8:435-440, particularly pp. 439-440). If this is incorrect, applicants are requested to clarify the record. As stated above, the specification fails to provide guidance regarding other

sources of media that comprise both chymosin and glucoamylase and guidance regarding how one is to incorporate chymosin and/or glucoamylase into the media of any mammalian, plant, bacterial, or yeast species. Furthermore, as the recited chymosin activity encompasses mutants and variants of chymosin polypeptides, it is noted that the specification fails to provide guidance as to how to make those variant chymosin polypeptides that are encompassed by the claims and still maintain the desired activity/utility.

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of producing a media from cultured cells was known in the art, the production of a media from the cultivation of any organism was not routine in the art. Further, while methods of generating variants of chymosin having a known amino acid sequence were known in the art at the time of the invention, *e.g.*, Li et al. (*Biochem Biophys Acta* 1384:121-129; cited in the Office action mailed 10/1/2004), it was not routine in the art to screen for *all* chymosin polypeptides having any number of substitutions or modifications as encompassed by the claims and screen and isolate those that have the desired activity/utility.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, and the high degree of unpredictability as evidenced by the prior art, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims.

The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

[11] The rejection of claims 1, 5-6, 9-10, 13-14, 16-18, 29-31, and 35 under 35 U.S.C. 102(b) as being anticipated by Uren et al. (US Patent 4,721,673) as set forth in the Office action mailed 10/1/2004 is withdrawn in view of applicants' amendment and arguments.

First, it is noted that the pH of the buffer used in the method of Uren et al. is "about 2.0." According to MPEP 2131.03, the pH value of Uren et al. does not anticipate the range of pH values as recited in the claims. Second, as noted above, the examiner can find no evidence of glucoamylase activity in the medium comprising chymosin of Uren et al.

Claim Rejections - 35 USC § 103

[12] The rejection of claim(s) 1, 5-6, 9-14, 16-18, 29-31, 35-36, and 42 under 35 U.S.C. 103(a) as being unpatentable over Ward et al. in view of Uren et al., Li et al., and

Pedersen et al. as set forth in the Office action mailed 10/1/2004 is withdrawn in view of the amendment to the claims.

The rejection has not been withdrawn in view of applicants' arguments, which are not found persuasive. Instead, the rejection has been withdrawn in favor of a new rejection (see below), particularly in light of applicants' amendment to remove a time limitation and to change the values of the ranges of pHs to which the medium is subjected in claim 1.

[13] Applicants' statement regarding disqualification of the reference of Kappeler et al. (US Patent Application Publication 2002/0164696 A1) is acknowledged. MPEP 706.02(1)(2) states, "[t]he common ownership must be shown to exist at the time the later invention was made. A statement of present common ownership is not sufficient." In this case, applicants have provided sufficient evidence that the common ownership existed at the time the later invention was made as follows: "this application (09/779,560) and Kappeler were, at the time the invention of this application (09/779,560) was made, owned by Chr. Hansen A/S" (page 7 of the response filed 1/3/2005). As such, the rejection of claim 39 under 35 U.S.C. 103(a) as being unpatentable over Ward et al. in view of Uren et al., Li et al., and Pedersen et al. as applied to claim(s) 1, 5-6, 9-14, 16-18, 29-31, 35-36, and 42 above and further in view of Kappeler et al. as set forth in the Office action mailed 10/1/2004 is withdrawn.

It is noted that applicants argue the combined references of Ward et al., Uren et al., Li et al., Pedersen et al., and Kappeler et al. fail to establish a *prima facie* case of obviousness of claim 39 for reasoning directed to the obviousness rejection of claims 1,

5-6, 9-14, 16-18, 29-31, 35-36, and 42. However, in order to clarify the record, it is noted that the examiner has withdrawn the rejection solely in view of the disqualification of Kappeler et al. as prior art and not in view of applicants arguments addressing the obviousness rejection of claims 1, 5-6, 9-14, 16-18, 29-31, 35-36, and 42. The examiner fully disagrees with applicants' arguments and if it is found that the reference of Kappeler et al. cannot be disqualified as prior art, a prior art rejection of claim 39 may be re-instated using the reference of Kappeler et al.

[14] Claim(s) 1, 5-6, 9, 12-14, 16-18, 29-31, and 42-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ward et al. (*Biotechnol* 8:435-440; cited in the IDS filed April 16, 2001) in view of Larsen et al. (WO 95/29999; cited in the IDS filed April 16, 2001). The claims are drawn to a method of providing a milk clotting composition comprising the active steps of providing a medium having a pH of 2.0 or greater that comprises chymosin and glucoamylase activities and subjecting the medium to a pH between about 1.0 and about 1.99 for a period of time sufficient to inactivate at least 50% of the glucoamylase activity while maintaining at least 75% of the chymosin activity.

The reference of Ward et al. teaches a method for recombinantly producing a *A. awamori* glucoamylase polypeptide fused to a bovine chymosin polypeptide by secretion of the polypeptide into the culture medium at pH 6 of *Aspergillus niger* var. *awamori* host cells expressing the fusion protein (see particularly pp. 436-438). Ward et al. teach treatment of the resulting medium with a pH of 2.0 for 30 minutes results in cleavage of the fusion protein into the individual chymosin/glucoamylase components

and further results in activating the chymosin (see particularly pp. 438-439). Ward et al. teach "the release of chymosin from the glucoamylase-chymosin fusion protein was favored at low pH" (p. 439). Ward et al. do not teach practicing their method at a pH below 2.0.

The reference of Larsen et al. teaches that prochymosin can be treated with an acid at a pH as low as 0.5 for conversion to the active form of chymosin (p. 10, bottom). As such, the prior art recognizes the treatment of chymosin at a pH of as low as 0.5.

MPEP § 2144.05 states, "[g]enerally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. '[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.' *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)." There is no evidence of record that would indicate that a decrease in pH from 2.0 to 1.99 is critical to achieve the desired level of glucoamylase inactivation while maintaining the desired level of chymosin activity and, absent evidence to the contrary, the method of Ward et al. is sufficient to achieve the recited level of glucoamylase inactivation while maintaining the recited level of chymosin activity. Also, there is no evidence of record that one of ordinary skill in the art would *not* have reduced the pH value of the medium of Ward et al. to pH of less than 2.0. The examiner acknowledges that numerous prior art references teach lowering the pH of a medium comprising the zymogen form of chymosin to a pH of 2.0 and not less (see, *e.g.*,van den Berg (*Biotechnol* 8:135-139), Goff et al. (*Gene* 27:35-46), Zhang et al.

(*Chin J Biotechnol* 7:169-175), and Parente et al. (*FEMS Microbiol Lett* 77:243-250). However, it is noted that the reduction in pH of the medium to 2.0 appears to be based on an attempt to "standardize" comparison of the resulting chymosin catalytic activity with studies of others. In this case, the claimed method is merely the method of Ward et al. using a workable range of pH treatment that was known in the art at the time of the invention as evidenced by Larsen et al.

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Ward et al. and Larsen et al. to practice the method of Ward et al. using a pH as low as 0.5. One would have been motivated to practice the method of Ward et al. at a pH of as low as 0.5 in order to determine whether pH values lower than 2.0 increase the amount of cleaved fusion protein or increase the rate at which cleavage of the fusion protein occurs, particularly in view of the teaching of Ward et al. that cleavage of the fusion protein is "favored at low pH." One would have a reasonable expectation of success for practicing the method of Ward et al. at a pH as low as 0.5 because of the results of Larsen et al. Therefore, claims 1, 5-6, 9, 12-14, 16-18, 29-31, and 42-43, drawn to a method of providing a milk clotting composition as described above would have been obvious to one of ordinary skill in the art.

The specification discloses "[t]ypically...the required treatment period is within the range of 0.1 minutes to 48 hours" (p. 7, lines 21-22). See also claim 18, which recites, "[a] method according to claim 1, wherein said period of time is in the range of 0.1 minutes to 48 hours." Based on this disclosure, it appears that a time of as little as 0.1 minutes at a pH of 1.99 will achieve the recited level of deactivated glucoamylase

while maintaining the desired level of chymosin. While the reference of Ward et al. does not teach that by practicing their method one can maintain the recited level of chymosin activity while inactivating the recited level of glucoamylase activity, absent evidence to the contrary, this is an inherent feature in practicing the method of Ward et al. at a pH as low as 0.5, as the low pH treatment of the method of Ward et al. is for 30 minutes, which is within the 0.1 minute to 48 hours time range disclosed as being sufficient for achieving the desired deactivation of glucoamylase, while maintaining the desired level of chymosin. Since the Office does not have the facilities for examining and comparing applicants' method with the method of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed method and the method of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald* et al., 205 USPQ 594.

RESPONSE TO ARGUMENT: To the extent applicants' arguments are pertinent to the instant rejection, these arguments are addressed below.

Applicants argue Ward et al. does not teach or suggest lowering the pH below 2 or that a reduction in pH may inactivate glucoamylase activity and thus, the references fail to establish a *prima facie* case of obviousness.

Applicants' argument is not found persuasive. In response to applicants' argument that Ward et al. does not teach or suggest lowering the pH below 2, there is no dispute that Ward et al. does not *specifically* teach lowering the pH below 2. However, Ward et al. clearly teach that the cleavage of the fusion protein is favored at low pH and the prior art recognizes that chymosin is active at a pH as low as 0.5.

Therefore, one of ordinary skill in the art would have practiced the method of Ward et al. at a pH below 2.0 in order to determine whether lower pH value results in increased cleavage of the fusion protein.

In response to applicants' argument that Ward et al. does not teach or suggest lowering the pH below 2 may inactivate glucoamylase activity, there is no dispute that Ward et al. does not teach or suggest lowering the pH below 2 may inactivate glucoamylase activity. However, absent evidence to the contrary, practicing the method of Ward et al. at a pH below 2.0 would inherently have inactivated glucoamylase activity to the recited level while maintaining the desired level of chymosin activity. MPEP 2144 states, "[t]he reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant." As such, it is not necessary that the art teach or suggest that one of ordinary skill in the art practice the method of Ward et al. at a pH lower than 2.0 to inactivate glucoamylase. In this case, one of ordinary skill in the art would have practiced the method of Ward et al. at a pH lower than 2.0 in order to determine whether an increased level and/or rate of cleavage of the fusion protein could be obtained.

Applicants argue data in the application "shows that by reducing the pH below 2.0, the glucoamylase activity is reduced significantly while the chymosin activity remains at a level of greater than 85%," referring to Tables 2.1 and 2.2. Applicants argue the prior art fails to teach or suggest this effect and asserts these results are unexpected advantages achieved by applicants' invention.

Applicants' argument is not found persuasive. It is noted that applicants' arguments addressing unexpected advantages at pH values of 1.6, 1.7, and 1.8 are not commensurate in scope with the claim limitations, which range from 1.0 to 1.99. In this case, there is no evidence of record that would suggest that by lowering the pH of a medium from 2.0 to 1.99 (a difference in pH of only 0.01) one would unexpectedly achieve the desired level of inactivation while maintaining a desired level of chymosin activity and that this desired level of glucoamylase inactivation cannot be achieved just as well by lowering the pH of a growth medium to 2.0.

Conclusion

[15] Status of the claims:

- Claims 1, 5-6, 9-14, 16-18, 29-31, 35-36, 39, and 42-43 are pending.
- Claims 1, 5-6, 9-14, 16-18, 29-31, 35-36, 39, and 42-43 are rejected.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (571) 272-0942. The Examiner can normally be reached Monday-Friday from 6:30 am to 4:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The FAX number for submission of official papers to Group 1600 is (571) 273-8300. Draft or informal FAX communications should be directed to (571) 273-0942. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

03-03-05

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PRIMARY EXAMINER